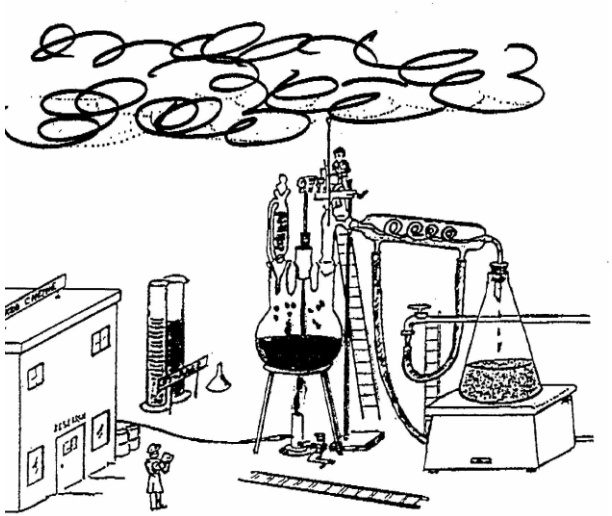
Design and Development of Viable and Sustainable Chemical Processes in the Pharmaceutical Industry

- Concepts, Challenges, Goals -



The lab results were so good we bypassed process development

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Lecture in the Drug Development Course

Royal Institute of Technology, 19th September 2018

EnginZyme

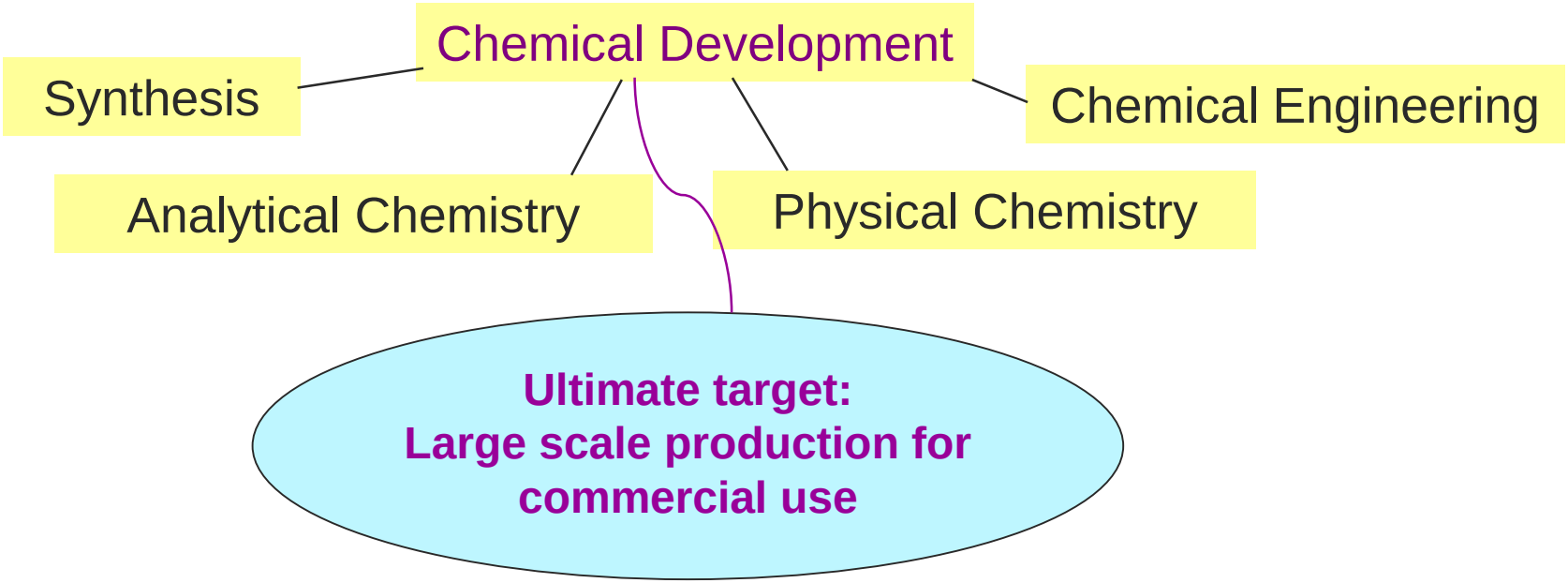
- Provider of proprietary enzyme technology established in 2014
- Located in a facility on the campus of the Royal Institute of Technology (KTH) in Stockholm, Sweden
- In a broad sense, business is about providing services in the biocatalysis area – i.e. use of enzymes for synthetic purposes
  - Unique platform operating on a solid support – porous glass beads
- Main customer focus: pharmaceuticals, agrochemicals, flavours & fragrances, water treatment

Engelmark Cassimjee, K.; Federsel, H.-J. *EziG: A Universal Platform for Enzyme Immobilization*. In "Biocatalysis: An Industrial Perspective"; de Gonzalo, G.; Dominguez, P., Eds.; RSC Catalysis Series No. 29, 2018; Ch. 13, pp 345-362

Topics

- Introduction – What is chemical process R&D?
- Taking laboratory chemistry to manufacturing scale
- Being alert to risks and hazards
- Synthetic chemistry & Route design
- Quality in the interest of the patient
- The era of Green Chemistry and Sustainability
- Summary & Outlook

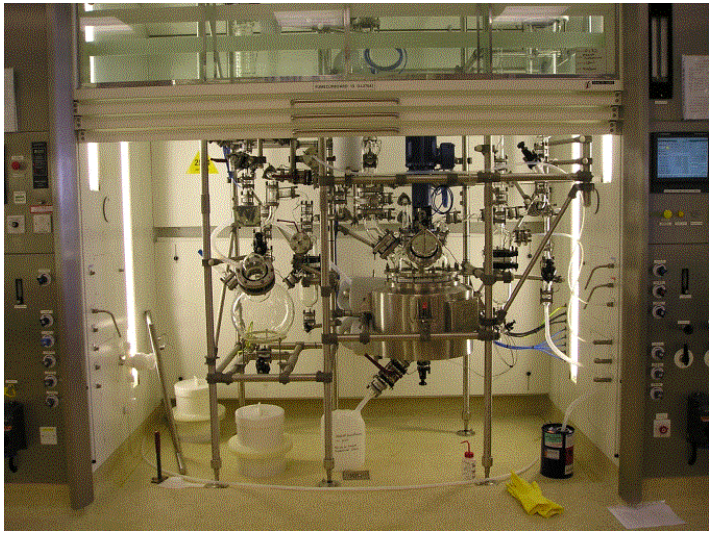
Start Small, Think Big

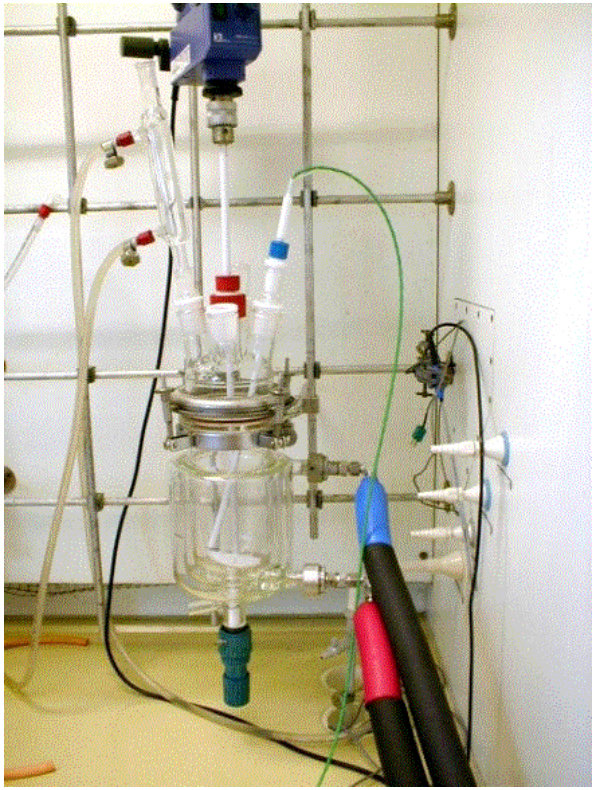


- Scope
  - To find the best route to prepare the Candidate Drug
  - Provide material for clinical evaluation
- Key activities
  - Evaluation of possible synthetic routes, including safety and environmental aspects, patent situation, cost
  - Optimization of the most favorable route

Federsel, H.-J. *Nature Rev. Drug Discov*. **2002**, *1*(12), 1013

Normal Work Environment in Process R&D

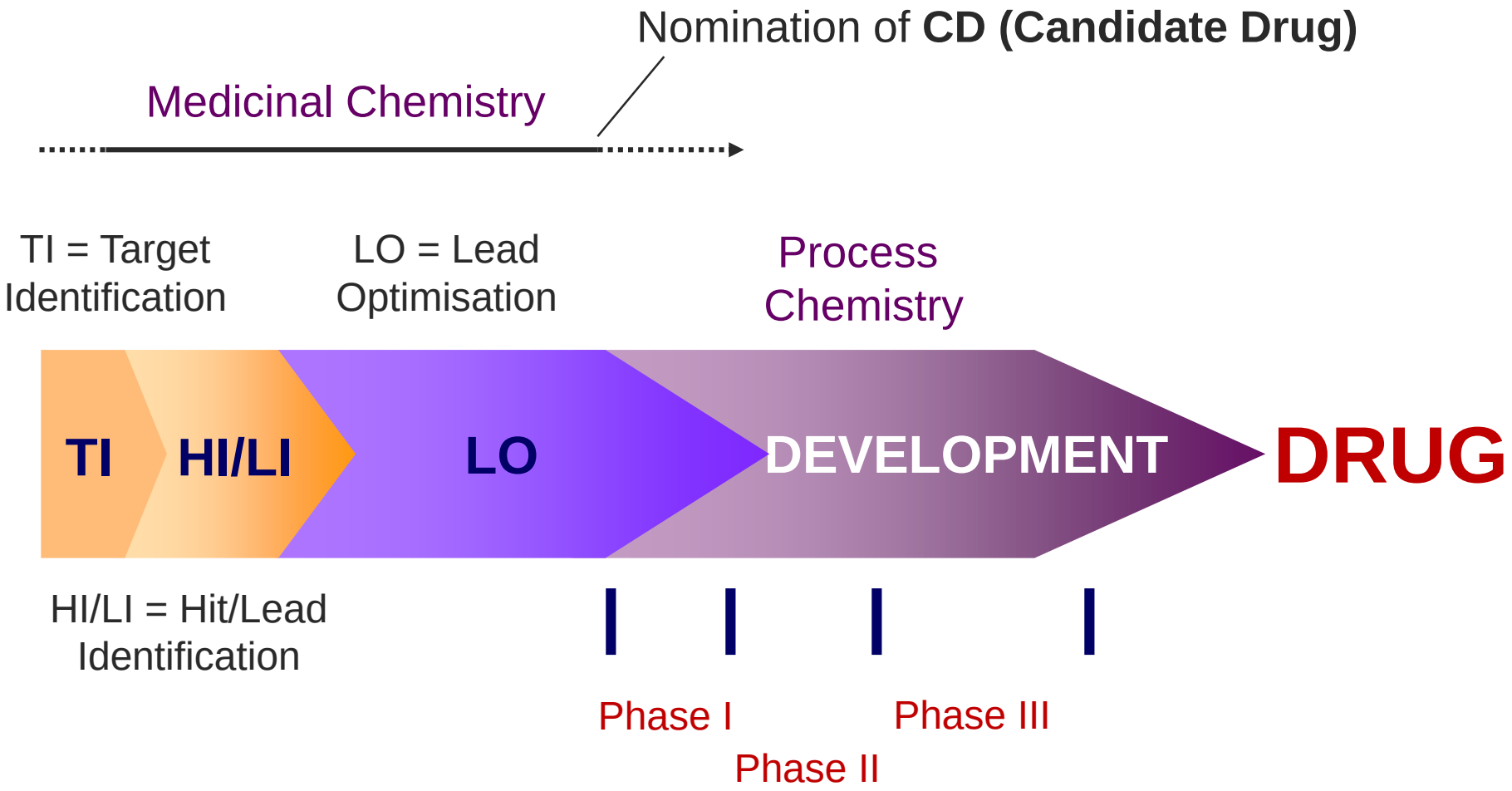




From Molecules to Processes to Patients

An Overview of a Long Journey

The Role of Chemistry



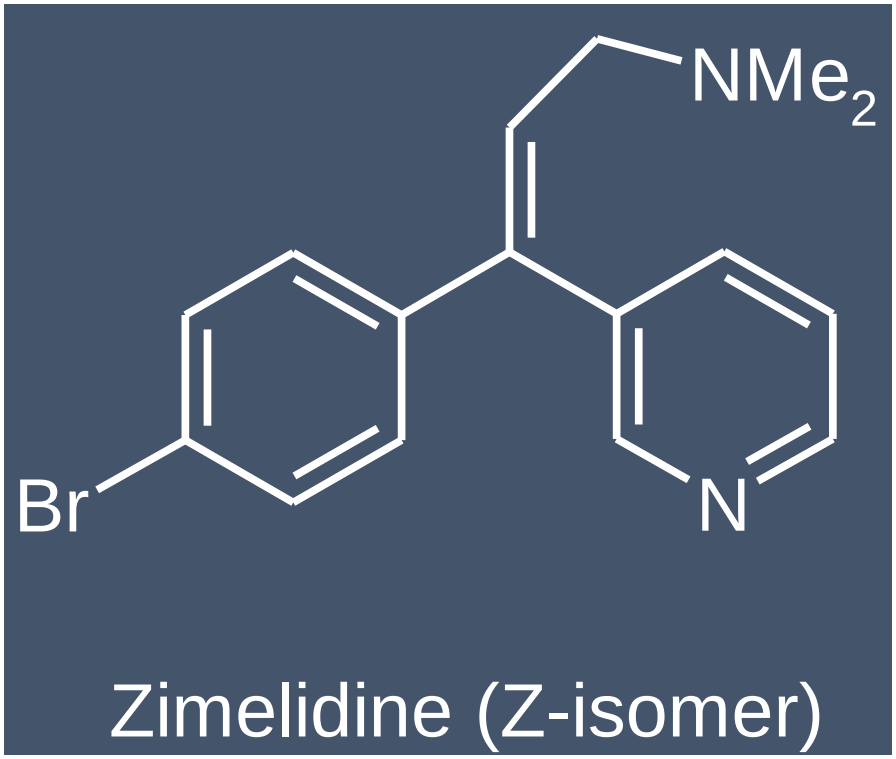
Chemists involved from early discovery phase to launch

Drugs in Three Molecular Classes

Dividing the chemical space according to molecular weight

- Small molecules – typically of molecular weight between 300-700D
- Large molecules – antibodies, proteins with M_W 20->100kD
- “Medium” sized – e.g. Oligonucleotides, antibody-drug conjugates with M_W 5-12kD and above

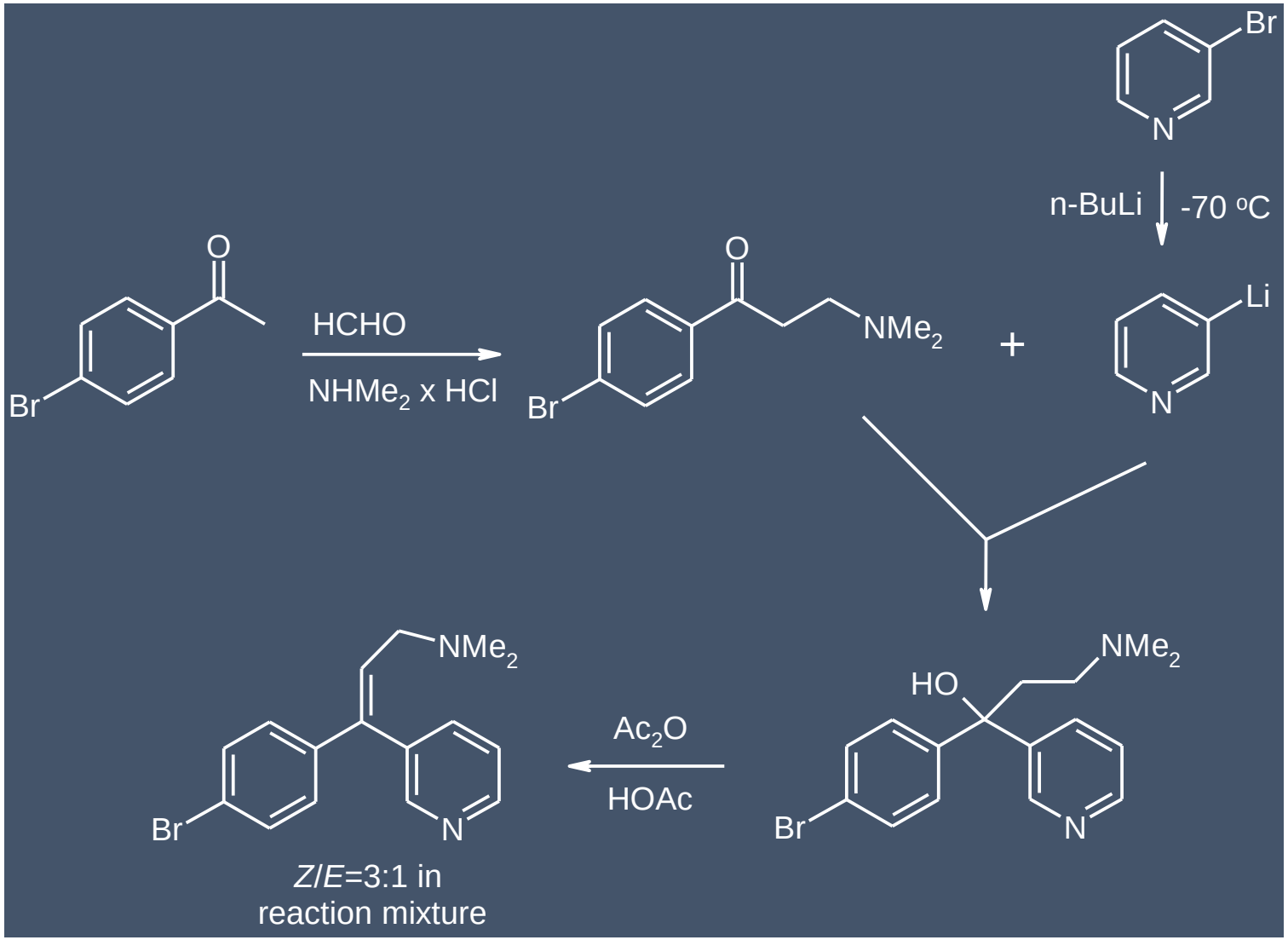
Where it all started……for me



Zimelidine (Z-isomer)

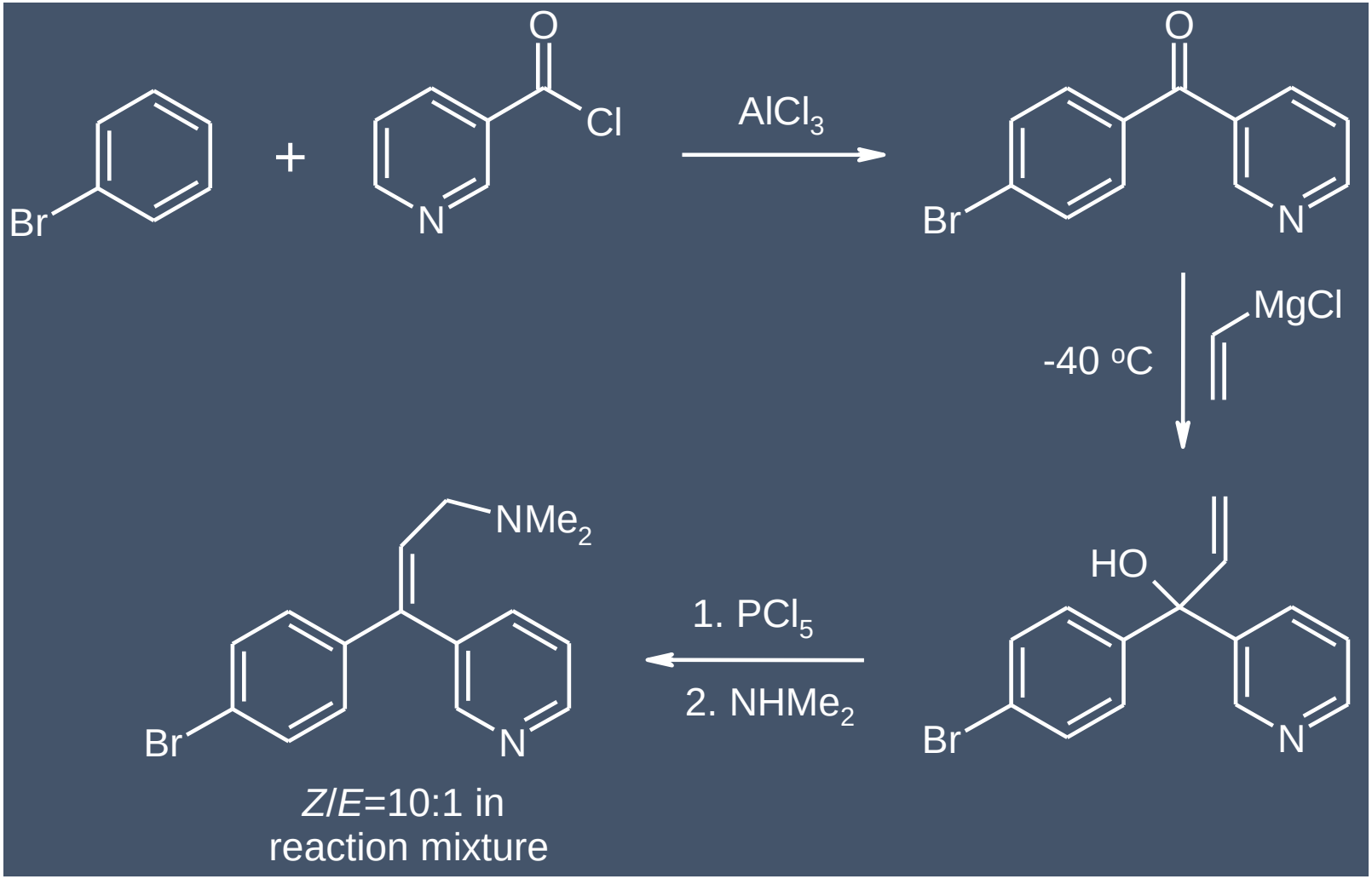
How was this molecule synthesized?

1st pilot scale approach

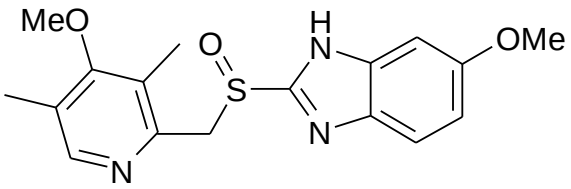


Federsel, H.-J. *Bioorg. Med. Chem*. **2010**, *18*(16), 5775-5794

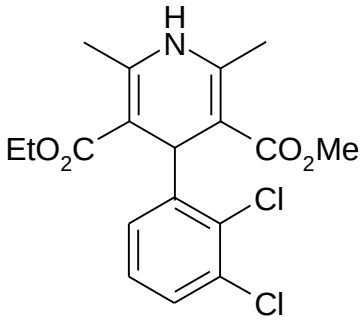
The commercial process



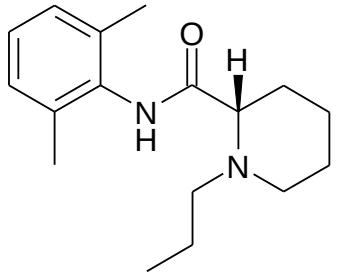
Molecules that Made It – Success Stories



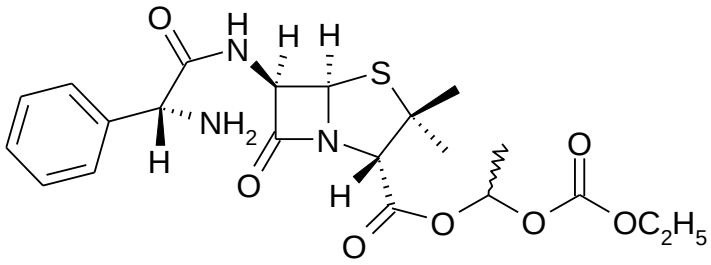
Omeprazole



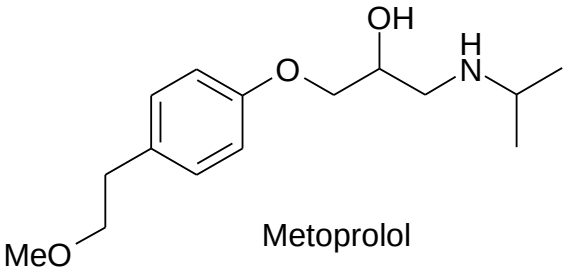
Felodipine



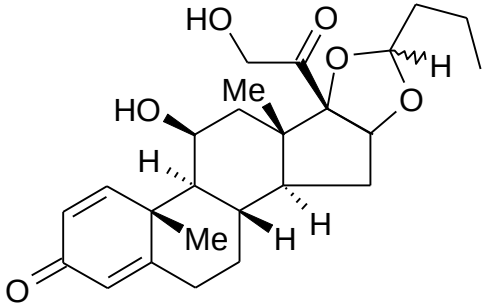
Ropivacaine



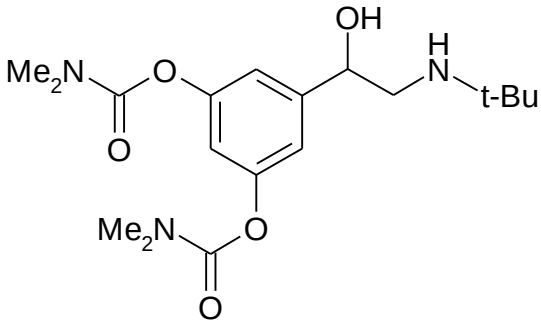
Bacampicillin



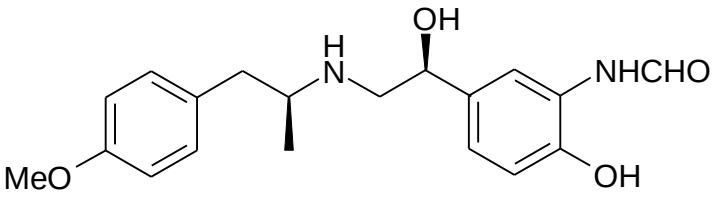
Metoprolol



Budesonide



Bambuterol



Formoterol

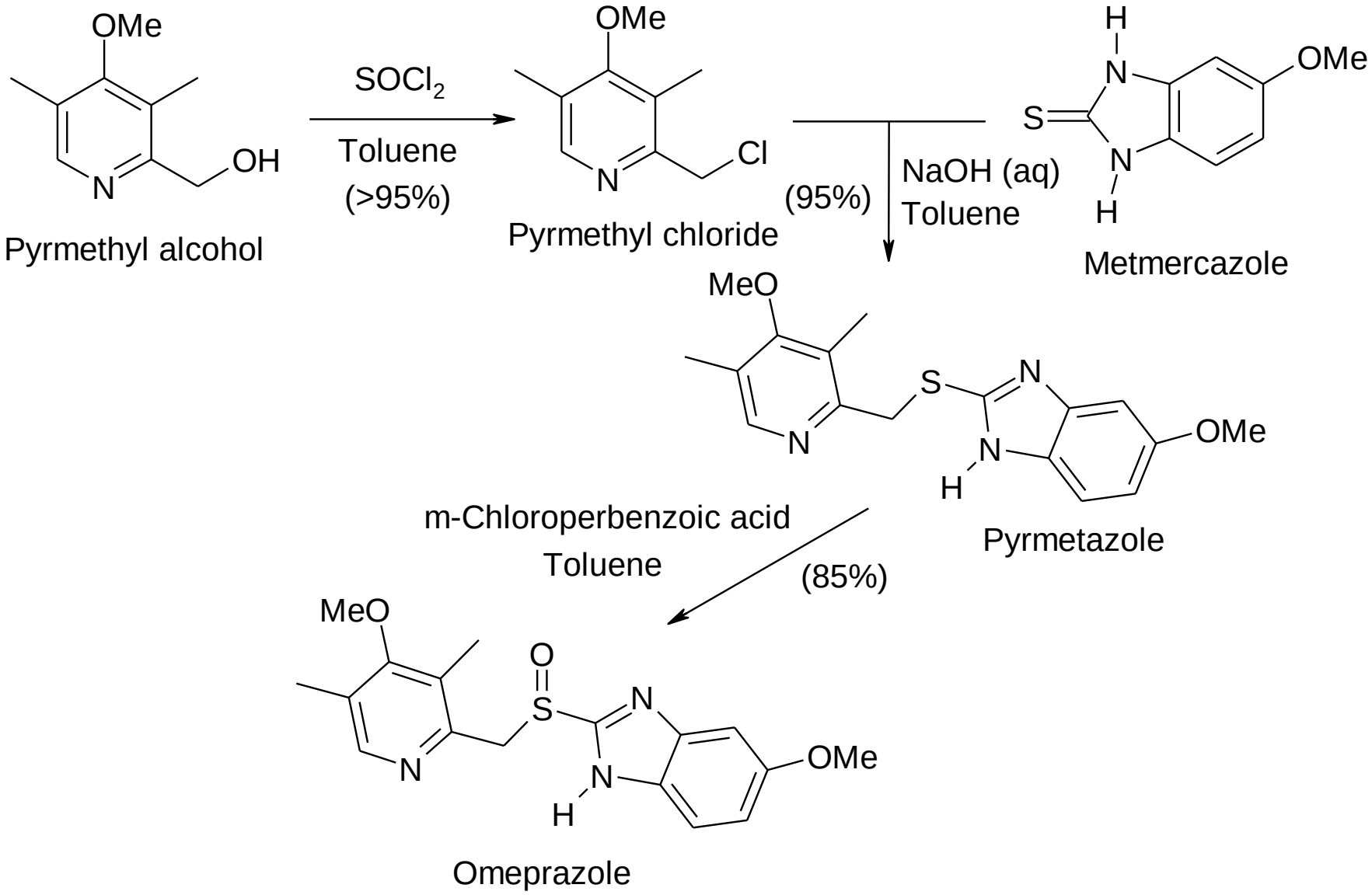
Structures of APIs (Active Pharmaceutical Ingredients)

Proton Pump Inhibitors – A Breakthrough in Therapy

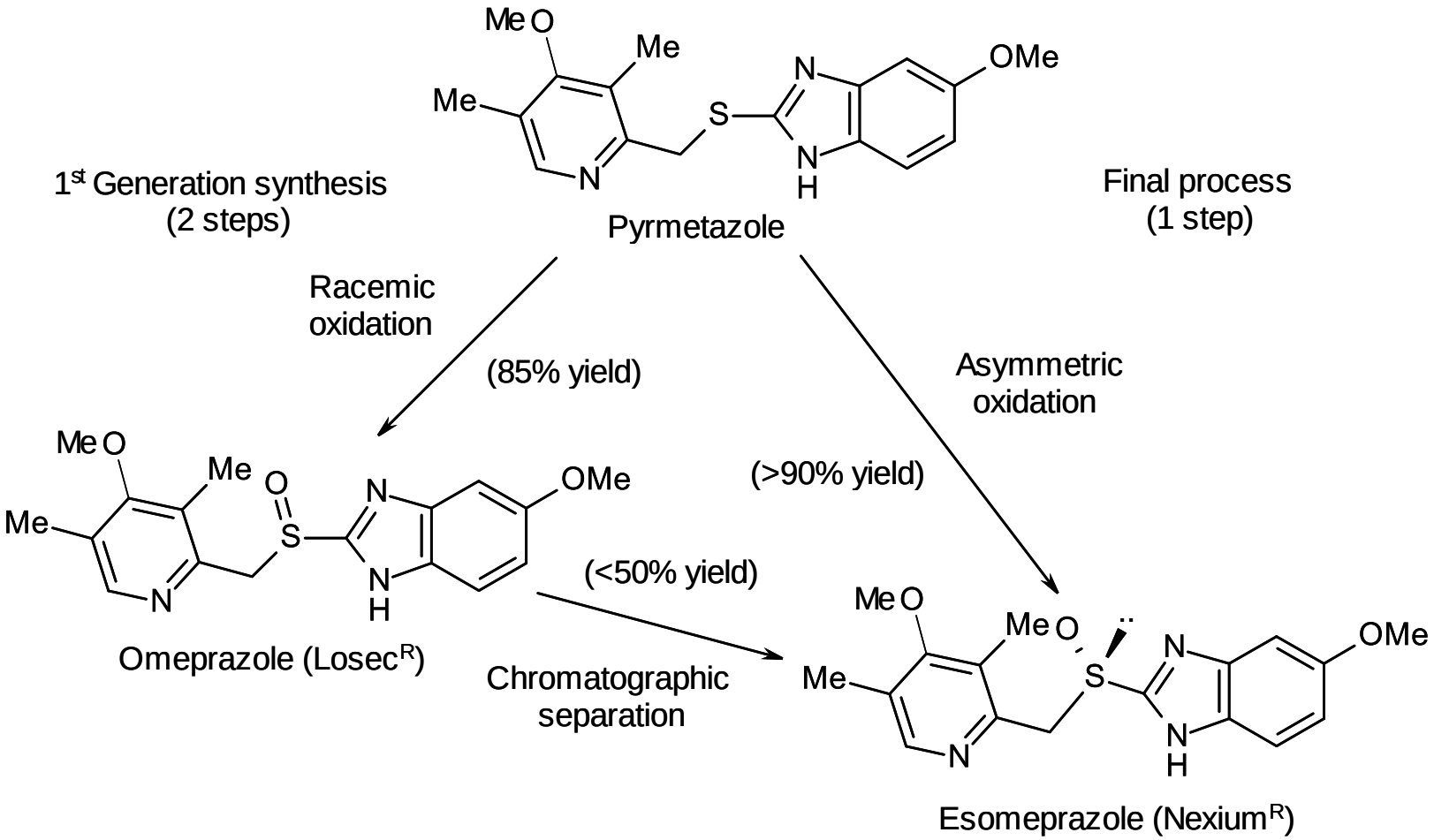
- In 1966 research was initiated at Hässle (part of Astra) in Mölndal (close to Gothenburg) focusing on gastrointestinal diseases, especially acid secretion in the stomach (peptic ulcer, Gastroesophageal reflux disease [GERD])
- Treatment paradigms in common use
  - Antacids, e.g. Alka Selzer, Salubrin
  - Surgical approaches
  - Novel medicines (cimetidin/Tagamet®, ranitidine/Zantac®) launched in the late 1970s; mechanism of action was antagonism of the histamine 2 receptor
- Understanding biochemical concept: A specific and unique enzyme - H^+,K^+-ATPase - responsible for generating acidic conditions (Sachs et al, 1977)
- First compound to be tested in man was inefficient (worked in rat model)
- Switch to dog model and focus on structure-activity studies
  - Long-lasting action; no aute toxicity; long-term side effects; patent issues
  - In Jan 1979 first synthesis of omeprazole
  - Fierce development and clinical testing including i.a. the design of a commercially viable synthetic route and a suitable formulation
  - Registration and launch of novel medicine in 1988 as Losec® (Prilosec® in the US)

Olbe, L.; Carlsson, E.; Lindberg, P. *Nature Rev. Drug Discov*. **2003**, *2*(2), 132-139

Commercial Manufacture of Omeprazole

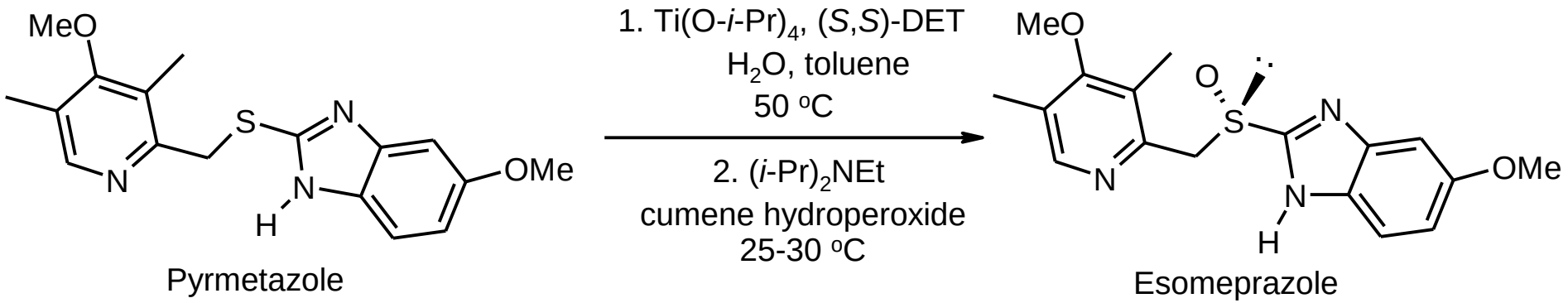


From Racemate to Single Enantiomer



Federsel, H.-J.; Larsson, M. In *Asymmetric Catalysis on Industrial Scale*. Blaser; Schmidt, eds; Wiley-VCH, Weinheim, 2004; pp. 413
Federsel, H.-J. *Nature Rev. Drug Discov*. **2003**, *2*(8), 654-664

High Performing Asymmetric Catalysis



Pyrmetazole

Esomeprazole

Key features

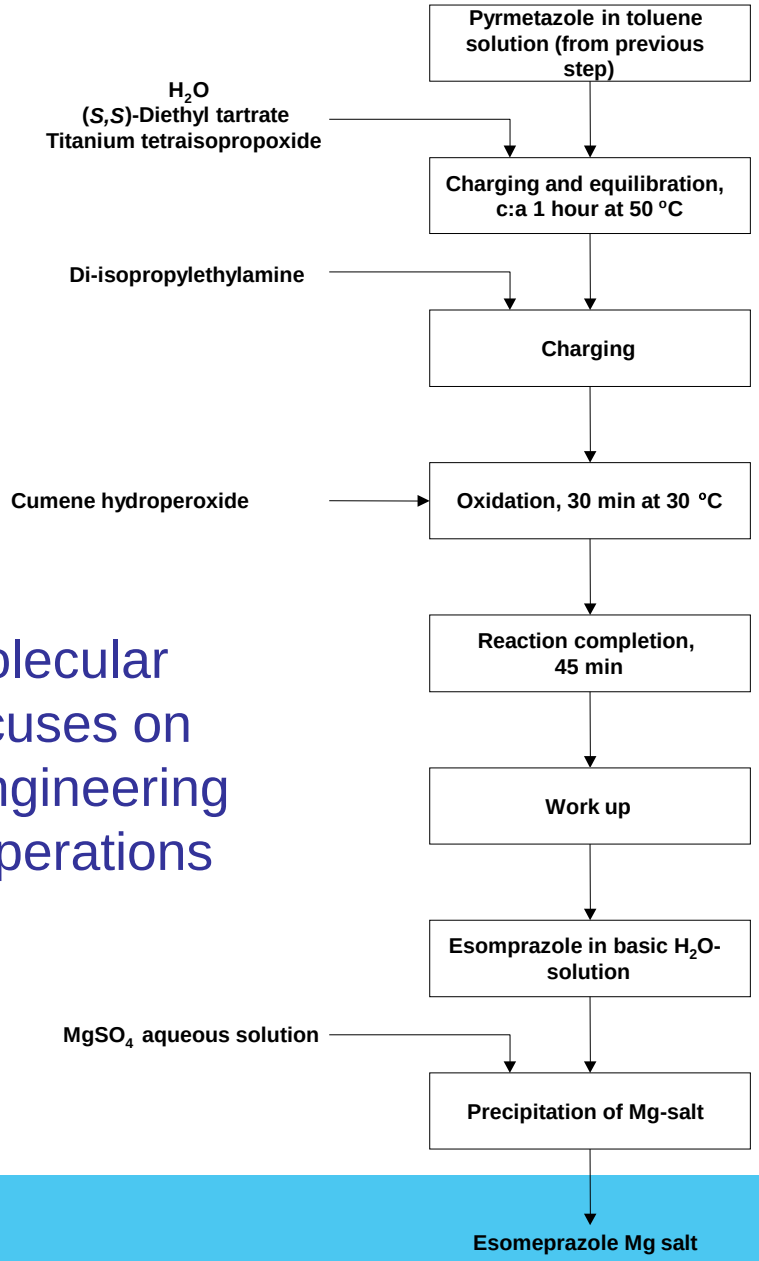
- Hünig's base – (*i*-Pr)$_2$NEt – essential
- Pre-formation of catalytic species required (step 1)
- Cheap oxidant
- Operative between 4-50 mol-% Ti

Process Validation

- Multi-hundred tonnes produced in excellent yield (>90%) and quality (>90% ee)

Seenivasaperumal, M.; Federsel, H.-J. et al. *Chem. Commun*. **2007**, 2187-2189
Seenivasaperumal, M.; Federsel, H.-J.; Szabó, K.J. *Adv. Synth. Catal*. **2009**, *351*(6), 903-919

Sulfoxidation Stage: Flow Chart



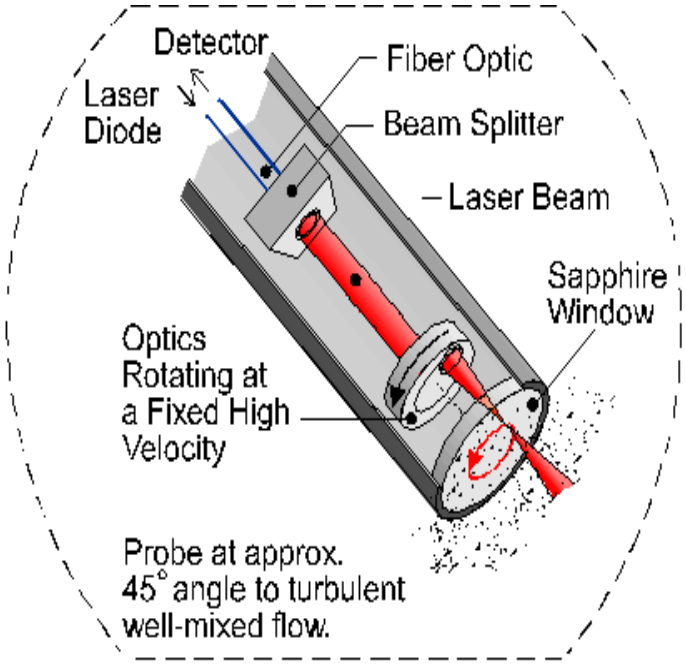
Takes out the molecular structures and focuses on process streams, engineering aspects and unit operations

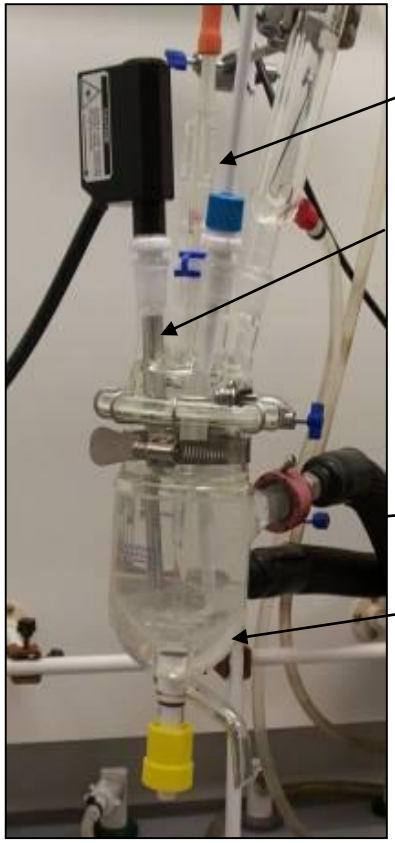
Crystallization in the Pharmaceutical Industry

- Essential to have robust crystallization processes
- Must be able to ensure product consistency and quality
- Important to maximise production efficiency
- It is estimated that 1/3 of pharmaceutical molecules are capable of forming hydrates
- Hydrate crystallization is more complicated and the factors controlling crystallization need to be understood
- Process Analytical Technology (PAT) is increasingly becoming employed to aid in the understanding and design of robust crystallization processes

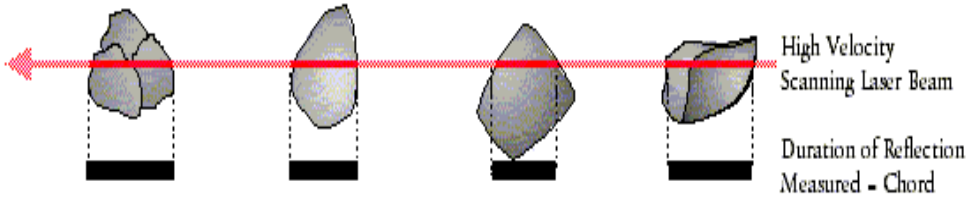
Stahl, H.P. Towards Better Safety of Drugs and Pharmaceutical Products, Ed. D.D Braimer, Elsevier/North Holland Biomedical Press, Amsterdam, 1980

Focused Beam Reflectance Measurement





The FBRM, or Lasentec, has a laser beam that rotates and when it hits a particle, the light back scatters. The time of the back scattering is measured and turned into a chord length



Pharma Manufacturing

Facts about API production

- The volume of active substance produced for commercial use ranges from a few kg (high potency, rare diseases) to several 100 tonnes (antibiotics, NSAIDs)
  - During R&D the requirement is normally 10-100 kgs (pilot plant)
- In general, production is conducted in batch mode – you put all reactants, reagents, solvents etc into a reactor – normally on a 4-6000 L scale
  - Operating in a continuous mode (e.g. flow chemistry) is gaining momentum
- Strict GMP (Good Manufacturing Practices) regulation applies
- The previous practise where most of the active drug in bulk was made in-house has now changed in favour of extensive outsourcing

Making APIs – Desired Process Attributes

- Short
- Convergent
- Catalytic (element of the Green Chemistry framework)
- Atom efficient (do not use protecting groups)
- Amenable to telescoping (in situ/one pot operation)
- Minimizing number of solvent swaps
- Operable in water/tolerant to water
- Simple purification – preferably by extraction and/or crystallization
- Environmentally concerned
- Scalable
- Robust in performance (consistently offering predictable yield and quality)
- Guaranteeing that the highest quality attributes of the product are upheld
- Intrinsically safe
- Freedom to operate (no patent or Intellectual Property [IP] issues)
- Cost conscious

Incident – Chemical Reaction Runaway

Thermal decomposition at Bayer Crop Science, West Virginia, USA in 2008 : 2 fatalities, 8 treated for possible toxic chemical exposure

Definition and Cause

The hazards associated with uncontrolled chemical reaction resulting in damage and potential injury

Most incidents occur due to

- A basic lack of understanding of the Process Chemistry and Thermochemistry
- Inadequate engineering design for heat transfer
- Inadequate control systems and safety back-up systems
- Inadequate operational procedures, including training

Scale and Safety

Chemical reaction hazards can occur at any scale from a laboratory experiment to large scale plant manufacture

Laboratory

Large Scale Laboratories
Pilot plants

Plant

Guanidine nitrate explosion
25 dead, 45 injured

With same chemistry

Safe(?)

Scale - up

Unsafe?

The amount of experimental testing and the detail required is to a large extent dependent on the scale of operation. Generally the larger the scale, the more information you require.

Homing in on Synthetic Chemistry

Designing the best route

A Diverse Set of Technologies

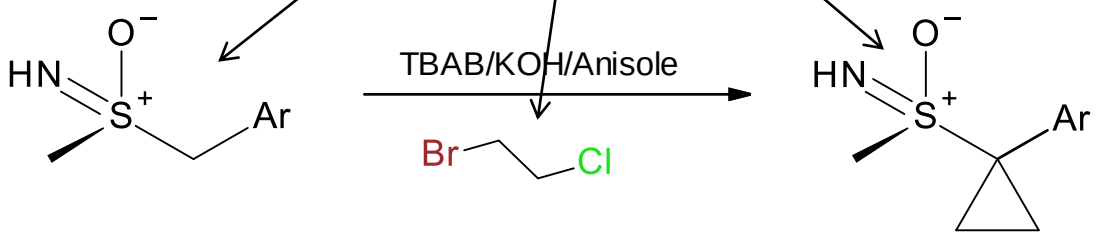
- Asymmetric transformations
  - Transition metal catalysis
  - Catalytic predictions
  - Biocatalysis is making strong inroads
- Cross-coupling reactions
  - Suzuki, Heck, Buchwald-Hartwig etc
- Construction of complex molecular frameworks
  - Unconventional (complicated) heterocyclic motifs
- Process Intensification
  - Get maximum output per unit reactor volume
  - Continuous processing built on flow chemistry
    - A new paradigm with huge potential, but clear limitations
- Reaching sustainability by means of adopting Green Chemistry Principles
  - A major trend in API manufacture

Two Phase Cyclopropanation

Poor Stability

Two-phase system, difficult to mix

Degrade under batch reaction conditions

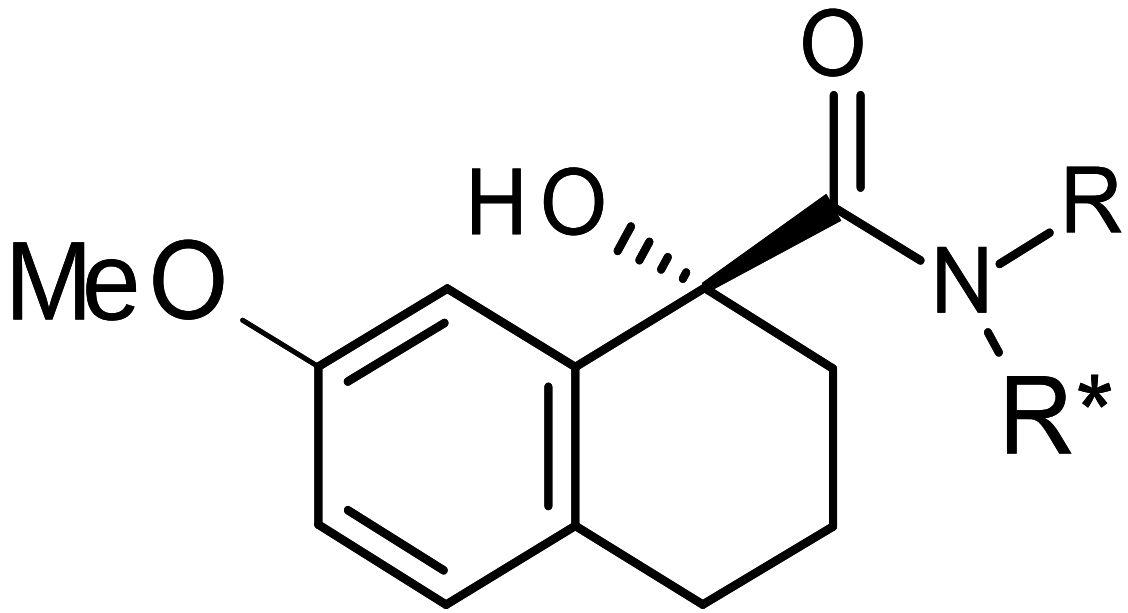


Non – robust process in batch 30-60% variable yield

- Control
- Fast reaction
- Improved mixing
- Flexible manufacture
- Substrate protected
  - Any problems and pumps can be stopped

Two successful Large Scale Laboratory manufactures (0.6 & 4 kg) at 74% yield; now ready to outsource!

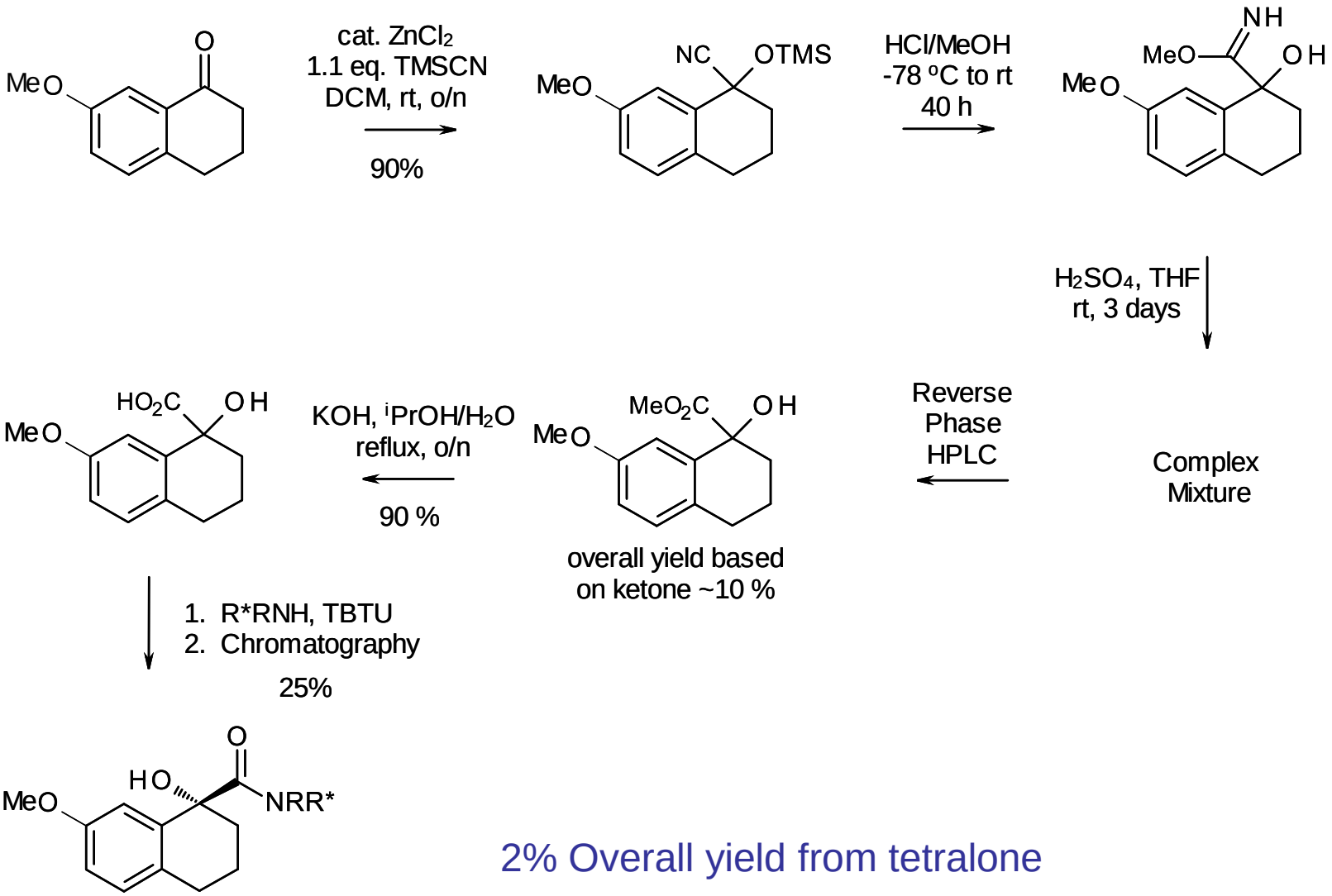
Route Design as a Key Feature



A promising class of key building blocks

Ainge, D. et al. *Org. Process Res. Dev.* **2003**, *7*(2), 198-201
Federsel, H.-J. *Acc. Chem. Res*. **2009**, *42*(5), 671-680

Medicinal Chemistry Route



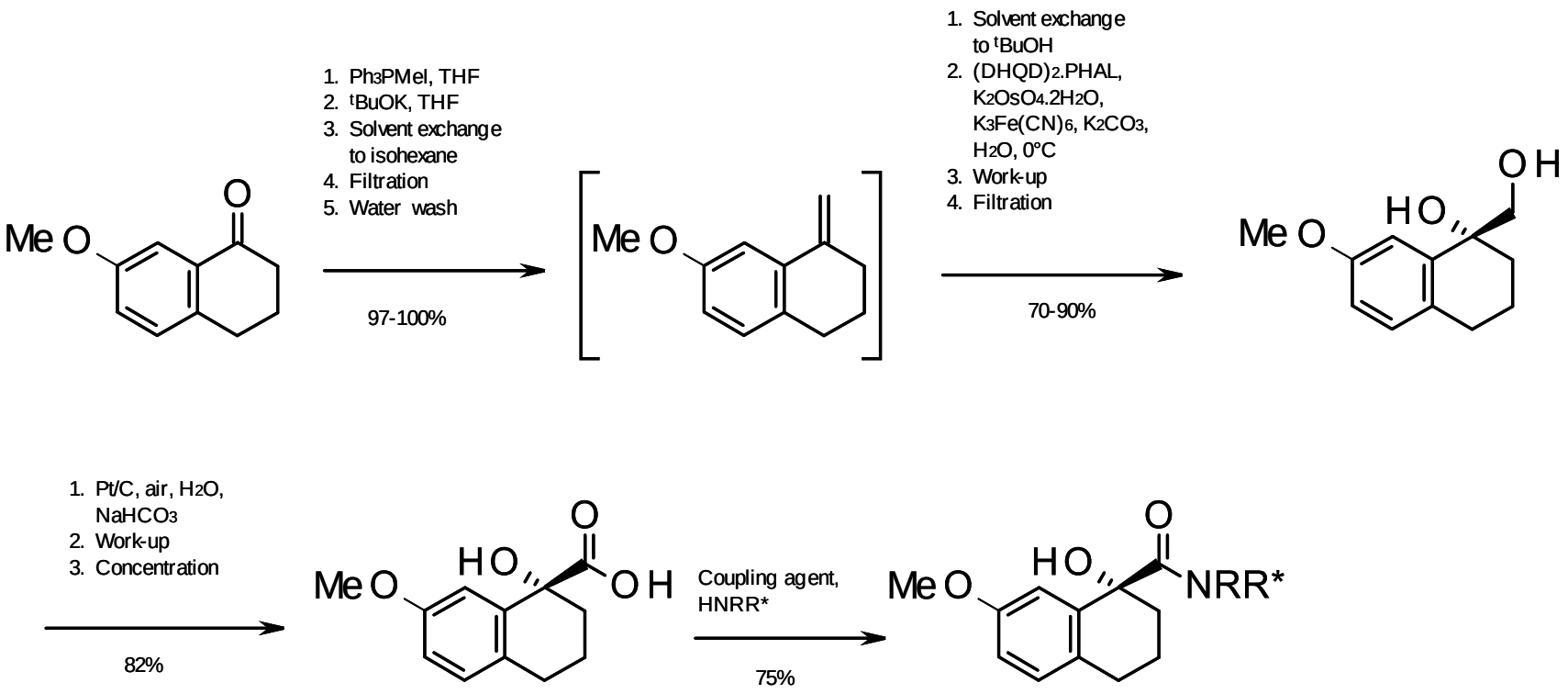
2% Overall yield from tetralone

Options

Several Options for delivery on scale

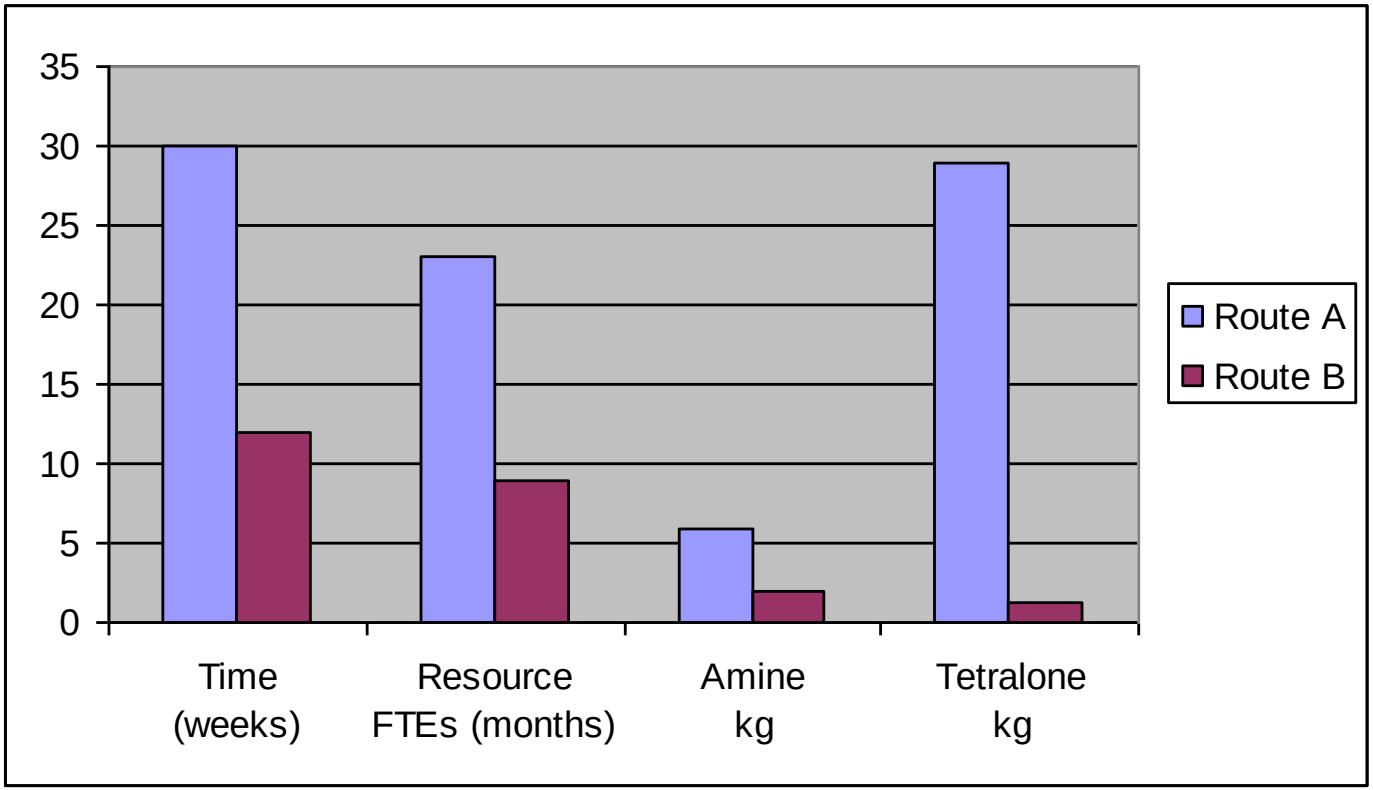
- Scale-up Med Chem route “as is”
  - Long predicted manufacturing times
  - Chromatographic isolation of desired enantiomer “unworkable”
  - Supply of chiral amine an issue
  - **Not viable**
- Modify Med Chem route
  - Potential for improvement of nitrile hydrolysis
  - Option to resolve racemic hydroxy ester or acid earlier in synthesis
    - Avoid chromatography in last step
  - Potential to effect asymmetric cyanohydrin reaction
    - Limited precedent with ketones
- Change route
  - Brainstorm identifies potential “winner”
  - Resource to focus on route change

A Smarter & Greener Method



42-55% Overall yield from tetralone

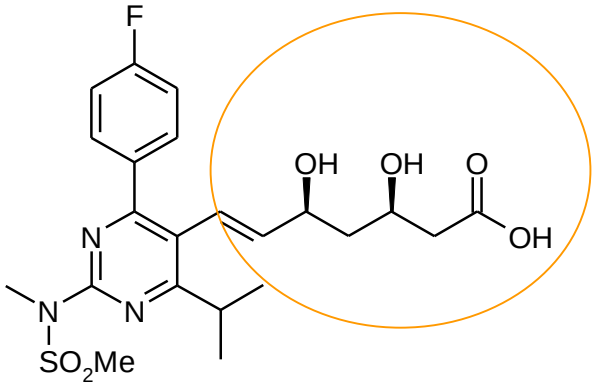
Comparing Routes



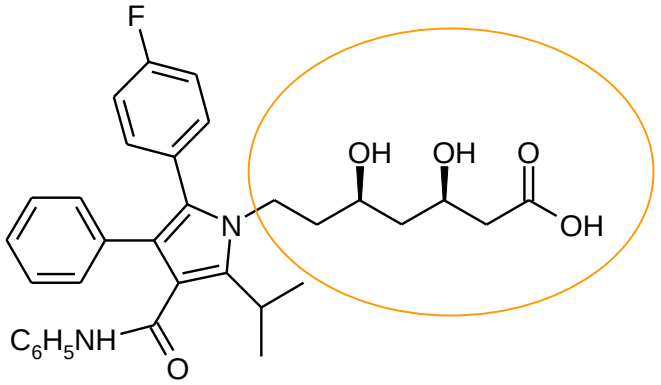
- Strong position to continue for next campaign
- Dramatic improvement in yield = reduced resource
  - Productivity
  - Efficiency
  - Environmental footprint

Biocatalysis: An Important Tool

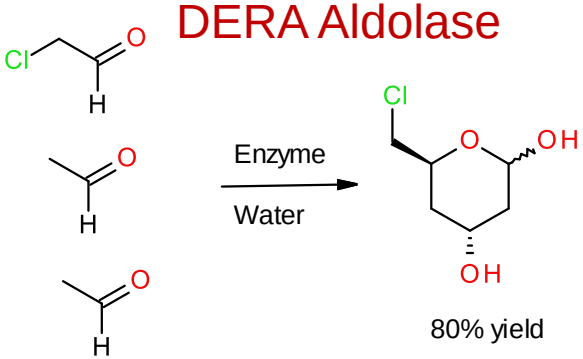
Rosuvastatin (Crestor® /AstraZeneca)



Atorvastatin (Lipitor® /Pfizer)

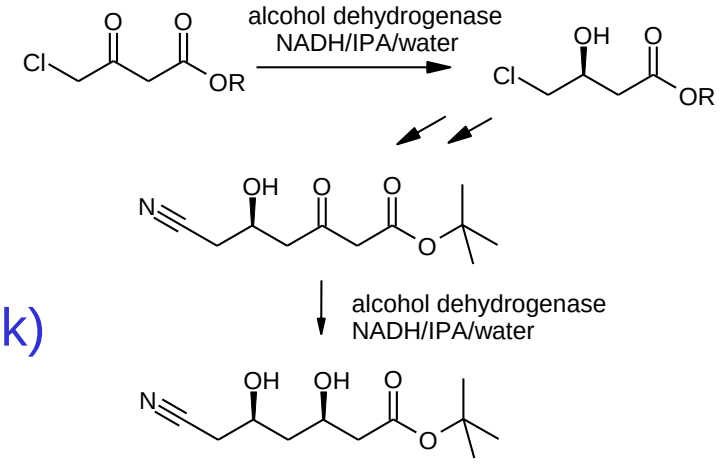


DERA Aldolase

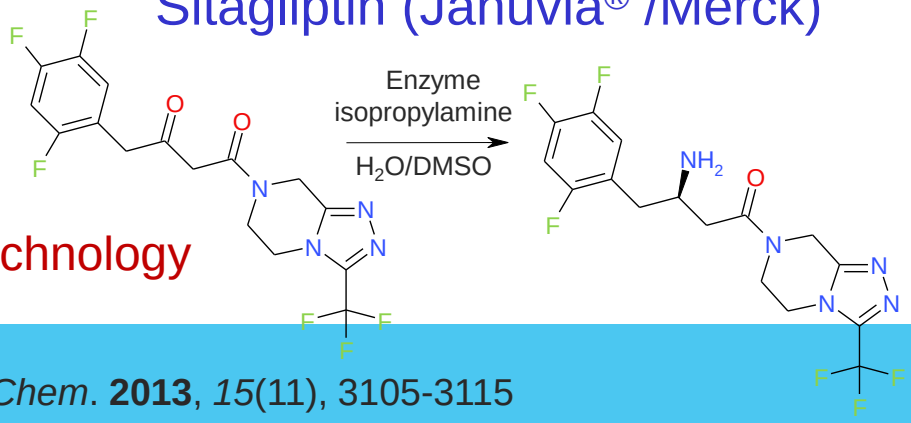


80% yield

Alcohol Dehydrogenase



Sitagliptin (Januvia® /Merck)



Transaminase technology

Federsel, H.-J. *Green Chem*. **2013**, *15*(11), 3105-3115

Quality Applied to Pharmaceuticals

The Historical Context

- The 1937 sulphanilamide catastrophy: Killed >100 children in USA due to ethylene glycol contamination of syrup formulation
  - Legislation put in place requiring government approval of all medicines prior to sale
- In 1946 the PMA [Pharmaceutical Manufacturers Association] published a guideline for GMP for Pharmaceuticals triggered by the introduction of antibiotics produced by fermentation on the market
- The 1959 thalidomide tragedy: Birth of many children in Europe with severe malformations of extremities
  - GMP is added to the Food, Drug and Cosmetic Act in 1962

The GMP Framework

Bulk actives (APIs) and drug product are governed by the Food, Drug and Cosmetics Act (1938) and are, therefore, required by US law to be produced in compliance with cGMP

- Quality and GMP puts the customer (=patient) in the center
- Therefore we need to ensure that medical products are consistently manufactured to the required quality
- GMP covers the whole value chain: From delivery of raw materials to release of finished product
- The principles of GMP concern: People, Premises, Processes, Products, Procedures and Profit
- GMP is part of QA that deals with the creation and operation of standards, procedures and management systems to guarantee the quality of a product throughout its life cycle

Homing-in on Quality

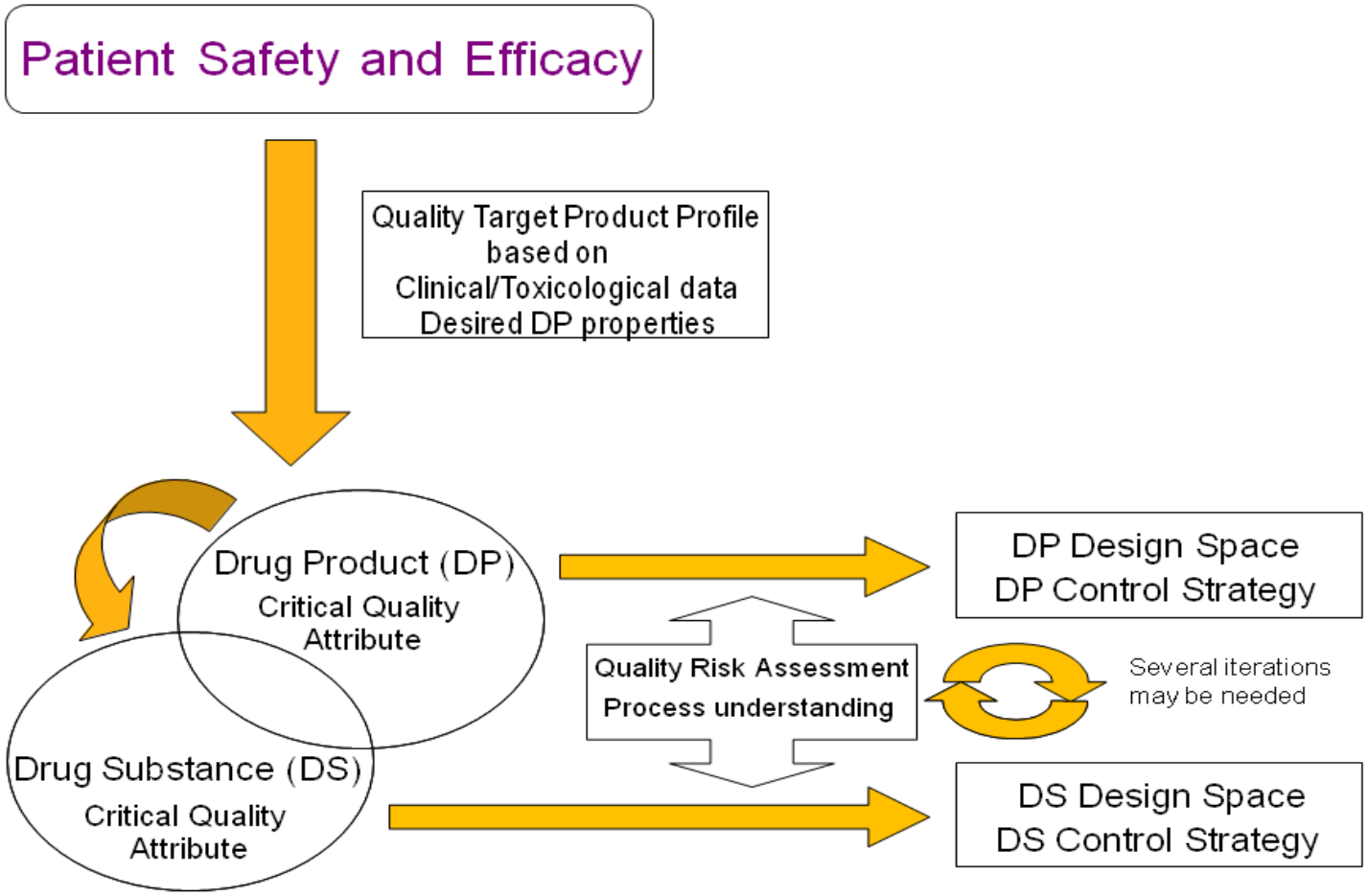
- Analytical Control as the approach before 1965
- Quality Control emerged in 1965-1970
- This was developed into GMP which started to be operated in parallel between 1970-1975
- Quality Assurance saw its start around 1975 and is in use ever since, albeit undergoing continuous change and updates
- Quality by Design principles have started to be implemented in the beginning of the 21st century

The Rationale for Quality by Design (QbD)

- Enables development work to be performed in a more efficient and streamlined way
- Provides opportunities for developing more reliable and robust processes and products and, as a consequence, delivers increased value to patients and the business
- Allows continuous improvement of manufacturing processes and control strategies throughout the product lifecycle with reduced need for post-approval changes

The Quality by Design Framework

The concept of QbD for Drug Substance and Drug Product



Courtesy Maria Edebrink & Talia Buggins, AZ Sweden/UK

Shades of Green

The Drive Towards Sustainability

The Concept of Green Chemistry

IUPAC definition

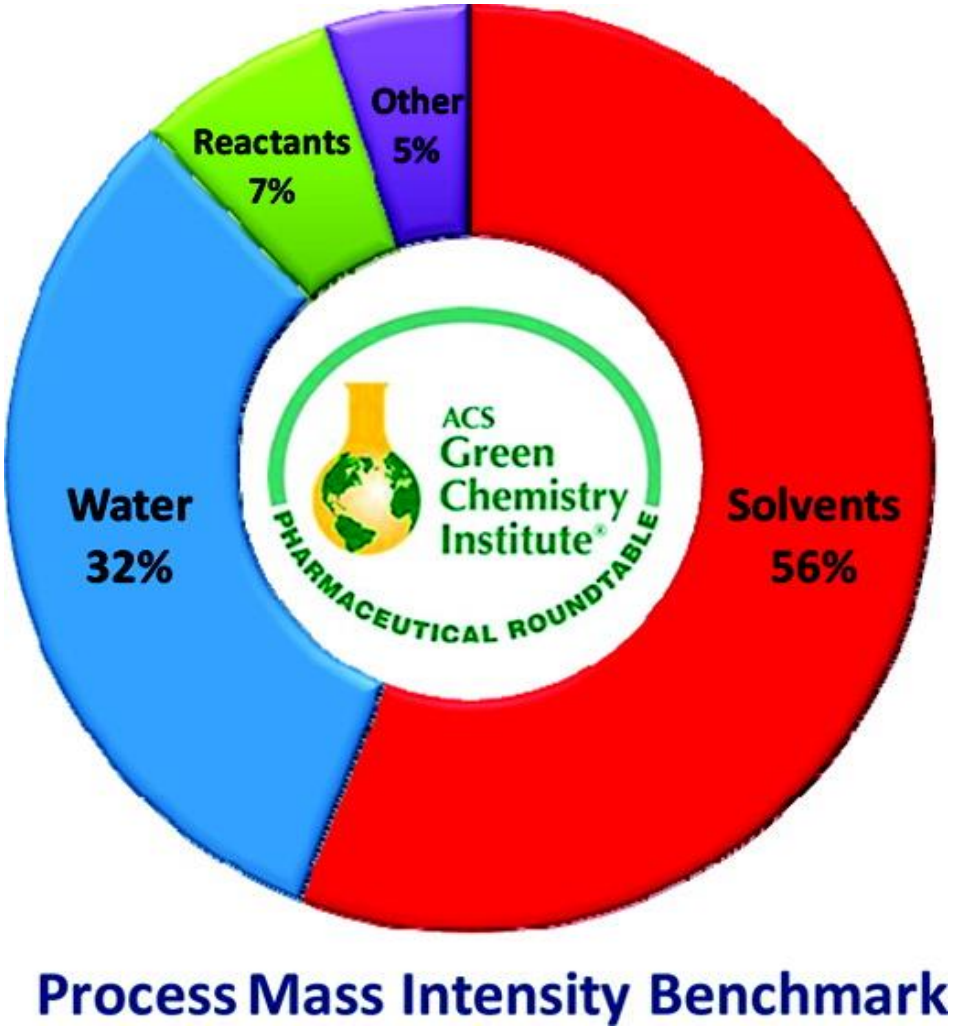
”The invention, design, and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances”

The 12 Principles of Green Chemistry

1) Minimise waste
2) Maximise reaction efficiency
3) Less hazardous synthesis
4) Safer reagents
5) Safer solvents
6) Energy efficiency
7) Renewable feed-stocks
8) Reduce derivatives
9) Use catalysis
10) Biodegradation
11) Real time analysis
12) Accident prevention

Anastas, P.T.; Warner, J.C. Green Chemistry: Theory and Practice; Oxford University Press, 1998
Anastas, P.T.; Kirchhoff, M.M. *Acc. Chem. Res*. **2002**, *35*(9), 686-694
Scalable Green Chemistry. Case Studies from the Pharmaceutical Industry; Koenig, S. G., Ed.; Pan Stanford Publishing, Singapore, 2013

Feedstock Composition for Making APIs



Jimenez-Gonzalez, C; Ponder, C.S.; Broxterman, Q.B.; Manley, J.B. *Org. Process Res. Dev.* **2011,** *15*(4), 912-917

Solvents – Volatile Organic Compounds (VOCs)

Active Pharmaceutical Ingredient (API) Manufacture

- Waste stream - 60-70% is solvents
- Energy usage - ~70% of attributed to solvent
- Natural resource utilisation ~80%
- Cost -10-40% is attributed to solvent

Cleaning

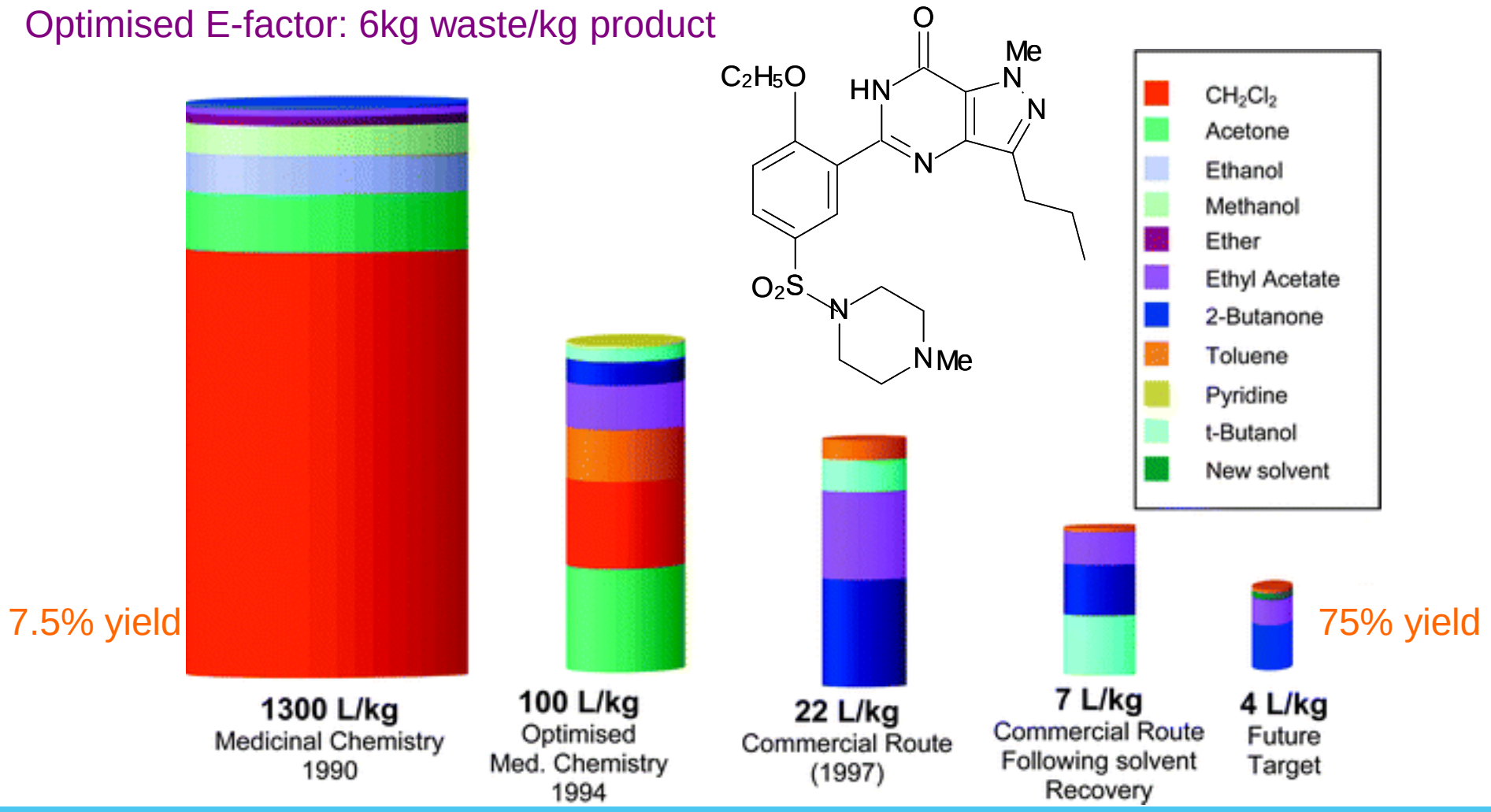
30-40% total VOC solvent use in pharmaceutical plant is used in cleaning! A 4,000L reactor uses ~5,000L solvent in a traditional cleaning process

Clean Tech. Environ. Policy **2005**, *7*, 41
EPSCR START **2005**
Green Chem. **2002**, *4*, 521

Efficiency in Solvent Utilization

Award Winning Green Chemistry to Pfizer (2003)
- The Sildenafil/Viagra® Case -

Optimised E-factor: 6kg waste/kg product



Dunn, P.J. et al. *Org. Process Res. Dev*. **2000**, *4*(1), 17-22; *Green Chem*. **2004**, *6*(1), 43-48

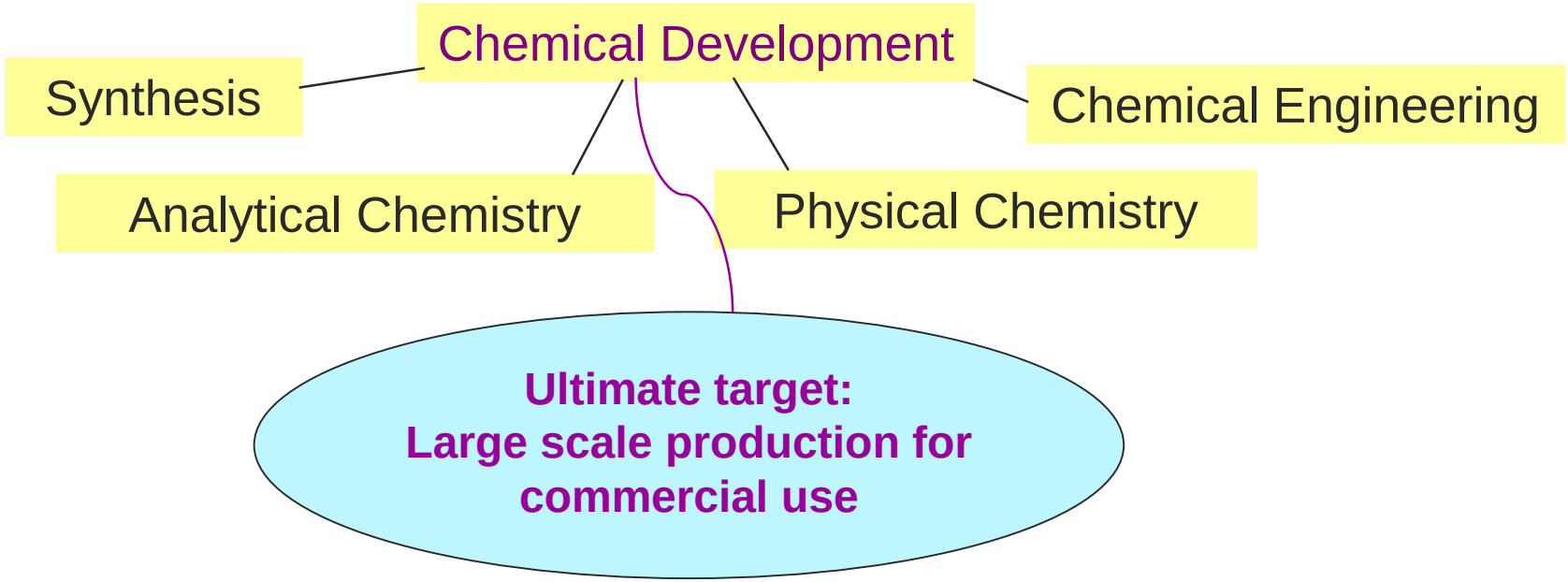
Becoming Green: Strategy & Technologies

- Identify risks and remove/minimise
- Minimise steps in the synthetic route
  - 4 steps will be greener & cheaper than 10 steps (most likely)
- Reactions in catalytic mode
- Minimise unit operations/energy usage
- Avoid isolations and drying
- Process intensification
- Consider recycle and reuse
- Effective abatement and waste treatment measures

Conclusions & Outlook

What I have been talking about

Take-home Message – Start Small, Think Big



- Guidelines
  - Keep the patient's needs in mind
  - Apply innovative thinking whenever possible
  - Use learnings from the past including findings from your peers
  - Chemistry is potentially dangerous – equip your process with safety by design features
  - Put sustainability on top of your priority list

Federsel, H.-J. *Nature Rev. Drug Discov*. **2002**, *1*(12), 1013